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The quest for planarizing distortions in hydrocarbons: two stereoisomeric [4.5.5.5]fenestranes

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ABSTRACT

According to semiempirical calculations the planarizing distortions in the central $C(C)_4$ substructure of fenestranes, represented as **1**, can be enhanced by a variety of structural modifications. Based on these results we selected the 7-hydroxy-c,c,c,c- and c,t,c,c[4.5.5.5]fenestranones **13** and **16** as precursors for the introduction of a bridgehead double bond. The efficient synthesis of these precursors and their chemical transformations are reported. Attempts to activate the hydroxyl group in **16** for introduction of a bridgehead double bond led to the rearrangement of the [4.5.5.5]fenestrane to a triquinacane skeleton.

1. Introduction

Ever since Hoffman et al. discussed some structural preconditions for hydrocarbons containing planar tetracoordinate carbon (ptC), this topic has received increasing attention.[1] Incorporation of the lone pair of planar tetracoordinate C into surrounding π-systems, replacement of the C substituents by other main group elements, the removal or addition of electrons to the valence shell, the incorporation of substructures into heteroatom ring systems are the most important results of this investigation.[1]

Theoretical, semiempirical as well as high level ab initio calculations have provided computational results for a wide variety of possible structures as 'stability islands' on the energy hyper surface. Since the review in 2006 by one of the authors providing an extended overview about the earlier endeavours,[2] many new results were reported; some of the important ones are recorded.[3–10] However, reports are scarce, for examples, where a combination of spectroscopic and computational analysis has led to experimental evidence for assemblies containing a tetracoordinate C atom in the gas phase.[11]

Special interest has found the question of the planarizing distortions in the $C(C)_4$ entities in the cyclic all-carbon fenestranes of type **1**.[12] Semiempirical explorations of structural features of a wide variety of these compounds led to concepts of how the opening of opposite bond angles in the corresponding central $C(C)_4$ substructures can be enhanced. This comprehensive analysis has shown that the introduction of bridgehead double bonds, inversion at one bridgehead and ring contraction are the most important tools to achieve this goal.

While our early computational MM2 analysis for the *cis*,*cis*,*cis*,-*cis*-[5.5.5.5]fenestrane[†] **3** gave opposite bond angles of α and β=113°, the recent DFT results yielded α and β=117° (C_1 symmetry).[1,13] The electron diffraction shows bond angles of 116° for α and β.[14] For the *cis*,*trans*,*cis*,*cis*-[5.5.5.5]fenestrane **4** containing a bridgehead with an inverted H the DFT-calculated bond angles are 125° and 116°, respectively.[13] According to the X-ray structure analysis of **15**, a derivative of **4** showed opposite bond angles of 131° and 120°, respectively.[15] Another derivative of **4**, containing a bridgehead substituent showed opposite bond angles of 134.9° and 119°.[16]

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[†] The stereoisomeric [5.5.5.5]fenestranes are specified by the configuration of the four bicyclic substructures starting with the 'upper' [4.5.0]bicyclooctane and [5.5.0] bicyloheptane substructure, respectively, in a clockwise manner.

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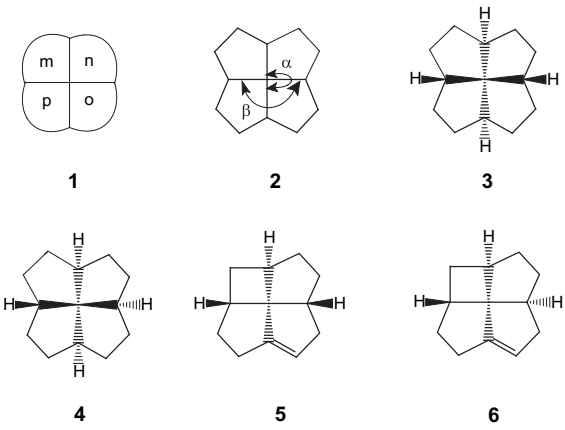


In continuation of our earlier endeavours, we selected the stereoisomeric [4.5.5.5]fenestrenes **5** and **6** as synthetic target molecules. The opening of the two opposite bond angles, specifically in *cis*,*trans*,*cis*,*cis*-[4.5.5.5]fenestrene **6** is due to the four-membered ring, the presence of a *trans*[5.5.0]bicyclooctane substructure and an additional bridgehead double bond. Our computational analysis by the DFT method gave bond angles of α=135°, β=129° for this compound, whereas α and β are 124° and 130°, respectively in the *cis*,*cis*,*cis*,*cis*-[4.5.5.5]fenestrene **5**.[13] The synthesis of **6** was particularly attractive since hitherto no compound of this structural type with opposite bond angles both >130° have been reported.

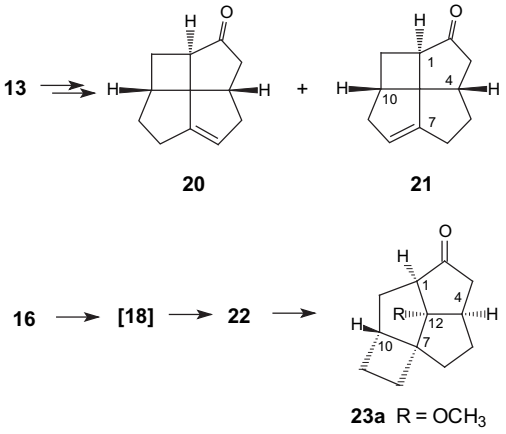
For introduction of a bridgehead double bond in the stereoisomeric [4.5.5.5]fenestranes we prepared functional derivatives of the c,c,c,c[4.5.5.5]- and c,t,c,c[4.5.5.5]fenestranone **13** and **15** and report here some of their chemical transformations.

2. Results and discussion

Our sequence for the preparation of the intermediate **8b** has been simplified (Scheme 1).[17] Instead of the reaction of 4-pentenoic acid chloride, derived from **7a**, with butenyl anions, **8a** was prepared by base induced condensation of ethyl 4-pentenoate **7b** in 57.5% yield.

Alternatively, the ketoester **8a** was prepared by γ,α-double allylation of ethyl acetoacetate. However this approach proved to be more tedious.[18,19]

Subsequent removal of the ester group and nucleophilic addition of ethine gave **9a**. As reported earlier, the Pauson–Khand reaction[20] of the diene-alkinol **9b** with its protected hydroxy group gave a mixture of the stereoisomeric bicyclo[3.3.0]octenones **10** and **11**.[17] Photocyclization of the pure stereoisomers gave the fenestranones **12** and **15** in 44% and 60% yield, respectively (Scheme 2).

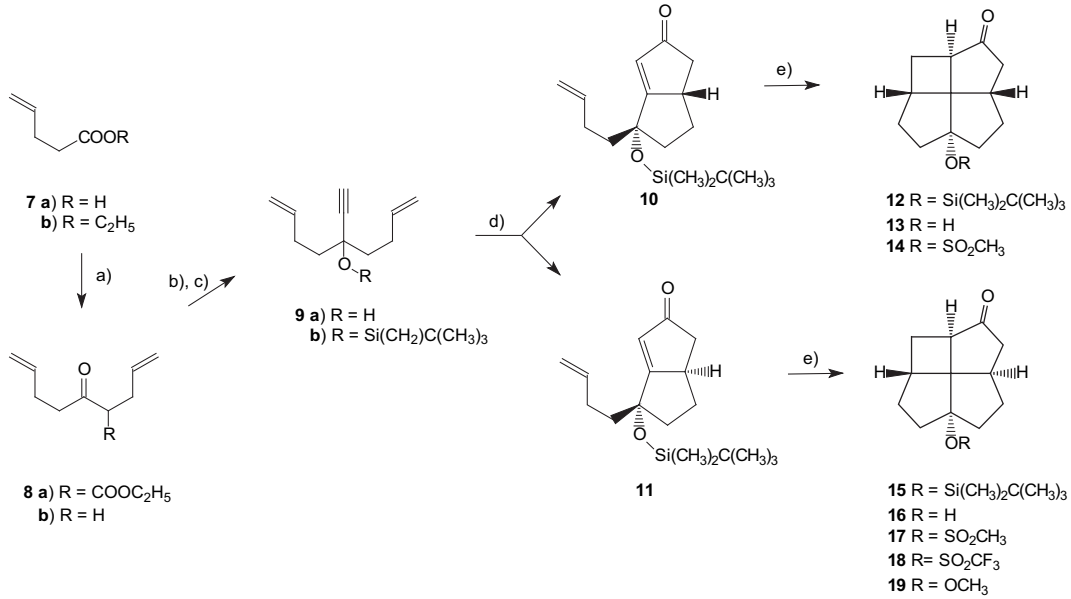


Scheme 2. Products formed by elimination reactions from the stereoisomeric hydroxyfenestranones **13** and **16**.

2.1. The *cis*,*cis*,*cis*,*cis*-[4.5.5.5]fenestrane series

The introduction of a bridgehead double bond extending from C(7) was first studied in the all-cis series. When the hydroxyketone **13**, readily obtained from **12**, was treated with mesyl chloride and base the two regioisomeric olefinic compounds **20** and **21** were formed directly in a 1:1 ratio with a total yield of 87% (Scheme 2). The expected mesylate **14** was not obtained under these conditions.

The overall structure of the regioisomeric [4.5.5.5]fenestrenones **20** and **21**, separated by HPLC, was established by 1D and 2D NMR measurements (Supplementary data, Tables 1 and 2).



Scheme 1. (a) NaH, $C_6H_5CH_3$; (b) NaOH; (c) HC≡CMgBr, THF; TBDMSi/OSO_2CF_3; (d) $Co_2(CO)_8$, NMO; (e) hν (254 nm), *t*-BME.

In the isomer **20**, the H at the bridgehead C(4) atom was identified by ^3J coupling with C(2)O. The $^3J_{C-H}$ interaction of C(4) with the vinylic H at C(6) provided unequivocal evidence for the structure of the regioisomeric fenestrenone **20**.

The H atom at C(10) was located via $^3J_{C-H}$ coupling of C(4) with H–C(10). The location of the double bond in **21** was apparent in the ^3J coupling between C(10) and the vinylic H at C(8).

2.2. The *cis*,*trans*,*cis*,*cis*[4.5.5.5]fenestrane series

When the hydroxyketone **16** with the cis,trans,cis,trans connectivity of the bicyclic substructures was treated with mesyl chloride under the conditions described above for *cis*,*cis*,*cis*,*cis*-isomer **13** a small amount (25%) of the mesylated compound **17** was obtained rather than the desired olefinic products. Reaction of the isolated, rather unstable mesylate **17** with DBU at rt gave a small amount of material, which according to ^{1}H NMR results did not show any signal at δ >4 ppm.

In a further attempt to enhance the formation of the desired bridgehead double bond we considered the triflate as a more reactive leaving group. The crude triflate, assumed to have the structure formulated as **18**, was obtained in 86% yield. When the triflate was treated with 2 equiv of Et_3N and 1 equiv DBU in CH_2Cl_2 at −5 °C for 3 h, no signals typical for a double bond were detected in the ^{1}H NMR spectrum of the crude product.

In order to trap the expected mixture of the isomeric bridgehead olefin to be formed from **16** via the triflate **18** the elimination reaction was performed with Et_3N and DBU in the presence of CH_3OH. This reaction was completed in less than 3 min at 0 °C. According to the ^{1}H NMR spectrum and MS analysis the product, isolated in 73%, showed the pattern expected for the structure of the 7-methoxy-[4.5.5.5]fenestranone **19**.

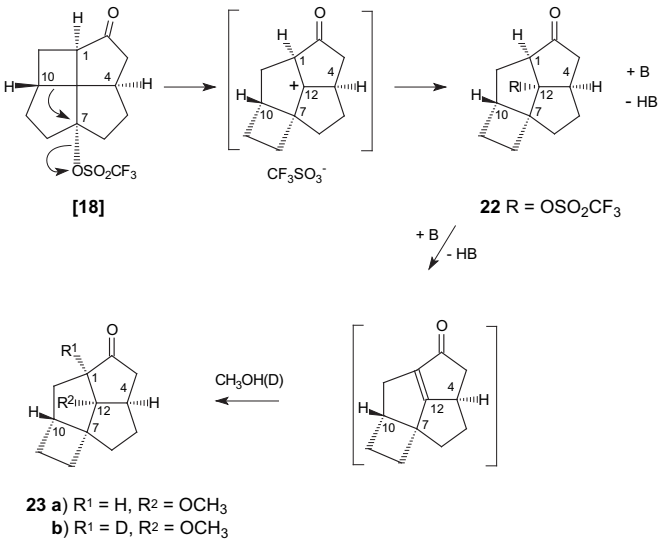
The COSY-2D NMR spectrum of this compound did not provide further clues for this structure. In order to solve the question whether this replacement reaction is a solvolysis or a 1,2 elimination followed by the addition of CH_3OH, the reaction was run with CH_3OD.

The product isolated contained this trapping agent. However, the ^{2}H atom was surprisingly located at the bridgehead adjacent to the CO group rather than at one of the CH_2 groups adjacent to the methoxy group at the tertiary position. Unless an unusual 1,3-elimination had occurred, this result was incompatible with the expected fenestrane structure **19**. A detailed 2D NMR analysis revealed that this compound containing the elements of CH_3OD has the structure of the bridged triquinacane[21] **23b** rather than 1-^{2}H-**19** (Supplementary data, Table 5).

First indications for this structure became apparent in a few $^2J_{C-H}$ and $^3J_{C-H}$ interactions in the HMBC spectra. Particularly noteworthy is the lack of $^3J_{C-H}$ interactions between the bridgehead positions C(4)–H(10) and vice versa C(10)–H(4). Also, there is no interaction in the $^3J_{C-H}$ 'emanating' from the quaternary C atom bearing the methoxy group and the H's at C(9). Conclusive evidence for the triquinane structure **23b** is based on the $^3J_{C-H}$ interaction between the quaternary C(12) bearing the methoxy group and the H's at C(3) (Supplementary data, Table 5). This coupling definitely excludes the fenestrane structure **19** (for clarity, the numbering of the fenestrane **18** in Scheme 3 was maintained for this triquinane derivative).

The mechanism for this at first surprising rearrangement is shown in Scheme 3.

Solvolysis of the fenestrane/triflate **18** leads via 1,2 rearrangement to a carbenium ion with triquinane structure, which gives the triquinane/triflate **22**. Base-induced elimination leads to the triquinane structure with a bridgehead double bond, which readily reacts with CH_3OD.



Scheme 3. A mechanistic pathway for the fenestrane/triquinane rearrangement.

Since the reaction of the 7-hydroxy-fenestrane **16** with Tf_2O was run in the polar CH_2Cl_2, stored at −20 °C overnight and worked up under aqueous conditions we suspected that the fenestrane/triflate **18** had already rearranged to the triquinacane/triflate **22** bearing the triflate at the bridgehead C atom in the β-position to the CO group. Indeed, the 2D NMR spectra of the crude triflate showed beyond doubt that we had the triflate **22** with the structure of a bridged triquinacane in hand (Supplementary data, Table 5). The evidence for this structure is based on the $^2J_{C-H}$ and $^3J_{C-H}$ interactions in the HMBC spectra. There is a strong $^3J_{C-H}$ interaction between the quaternary, triflate bearing C(12) and the H's at C(3). In addition no $^3J_{C-H}$ interactions are found between C(4) and H at C(10) and C(10) and the H at C(4). Also, there is no $^3J_{C-H}$ interaction between C(12) and the C(9)H2 expected for the fenestrane/triflate **18**.

The ready, base induced reaction of the triflate **22** in the presence of CH_3OD is therefore just a 1,2 elimination followed by a normal, regioselective 1,2-addition to give the substituted **23a** and **23b**, respectively.

3. Concluding remarks

The easy access of the *cis*,*cis*,*cis*,*cis*- and *cis*,*trans*,*cis*,*cis*-[4.5.5.5] fenestranones **13** and **16** in a few steps provides the starting material for introduction of bridgehead double bond at strategic locations. Surprisingly, the reaction of **16** with Tf_2O induced a rearrangement, which upon base-induced elimination in CH_3OH led to the triquinacane **23a** rather than to the expected fenestrenone with a $\Delta^{6,7}$- and/or $\Delta^{7,8}$-bridgehead double bond.[22] The attempts to introduce a bridgehead double bond in the *cis*,*trans*,*cis*,*cis*-[4.5.5.5]fenestrane with methyl groups in the 4- and 10-positions are presented in the accompanying paper.[23]

4. Experimental

4.1. General

Chemicals were purchased form commercial suppliers and used without further purification. BuLi (Fluka) was used as a 2.7 M soln in hexane, ethinyl-MgBr (Fluka) as a 0.5 M soln in THF. THF was originally dried by distillation from Na. Later, solvents for reactions were dried and purified by filtration over alumina (THF, CH_2Cl_2). For workup the reaction mixture was poured onto ice and ether or CH_2Cl_2, if necessary neutralized with a NaH_2PO_4 buffer, the organic

phase dried over $MgSO_4$). The crude product was analyzed by TLC and purified by flash chromatography (FC) or column chromatography (CC). Thin layer chromatography was performed on silica gel plates SIL G/UV_{254} (Macherey and Nagel). Visualization by staining with phosphomolybdic acid (0.5% in EtOH abs) and heating. IR (recorded on a Perkin–Elmer-782 IR-spectrophotometer) and NMR spectra (recorded on Bruker AC 300 [^{1}H, 300 MHz; ^{13}C, 75 MHz] and Bruker Advance II 400 [^{1}H, 400.13 MHz; ^{13}C; ^{2}H] were measured in $CDCl_3$ (locked to internal $CHCl_3$ (δ=7.27 ppm; δ=77.0 ppm for ^{13}C). ^{1}H/^{1}H and ^{1}H/^{13}C correlation experiments (COSY, HSQC, HMBC, NOE)) were used for signal assignments, respectively. Chemical shifts are given relative to $Si(CH_3)_4$ in δ (ppm) for the ^{1}H NMR, ^{13}C and ^{2}H NMR signals. Coupling constants are given in hertz and multiplicities are indicated as s (singlet), d (doublet) t (triplet), q (quartet), m (multiplet) and st (stack). Mass spectra (MS), determined on a Varian MAT CH7A (70 eV, EI) and a Fisons Autospec Q spectrometer, are reported in units of *m*/*z* and in relative intensities to the base peak.

TBDMS-triflat: *tert*-Butyldimethylsilyl-trifluoromethansulfonate (Fluka, purum, >98%), DBU 1,8-diazabyclo[5.4.0]undec-7-ene; NMO 4-methyl-morpholino-4-oxide, ethinyl-MgBr (Fluka, ~0.5 M in THF), Tf_2O: trifluoromethanesulfonic acid anhydride (Fluka, purum, >98.0%); Methanol (Merck, p.a.), methanol-d_1 (ARMAR Chemicals, 99.5 Atom% D). Ar was used for degassing the reaction mixtures. HPLC: NUCLEODUR VP 250/10, 100-5, (Macherey and Nagel), solvent: hexane/*t*-BME (19:1), flow rate: 4 mL/min, pressure: 1 MPa. MM2: molecular mechanics.[24] DFT: density functional theory method.[25]

4.1.1. 4-Carbonyloxyethyl-nona-1,8-dien-5-one ***8a***[26,27]. To the suspension of NaH (55–65% in oil; 48 g, 1.2 mol) in toluene (300 mL) kept at 90–100 °C there was added dropwise a solution of ethyl 4-pentenoate[28] **7b** (136 g, 1 mol) in toluene (100 mL). After heating for 2 h the cooled solution was treated with 12 mL ethanol, poured onto ice and extracted with ether. The organic phase was dried ($MgSO_4$), evaporated under reduced pressure and distilled under high vacuum to give 70 g (67%) of pure **8a**. Bp: 85–95°C/0.5 Torr.

4.1.2. Nona-1,8-dien-5-one ***8b***. A mixture of ketoester **8a** (70 g, 0.33 mol) and NaOH (26 g, 0.65 mol) in water (260 mL) was stirred vigorously overnight. Treatment with concd HCl (75 mL, 0.75 mol), extraction (2×) with ether and distillation in vacuo gave 42 g (91.3%) **8b** of bp 75–76°C/12 Torr.

4.1.3. 5-Ethinyl-nona-1,8-dien-5-ol ***9a***. A solution of the ketone **8b** (23 g, 0.167 mol) in abs. THF was dropwise added to a commercial solution of ethinyl magnesium bromide (390 mL, 0.5 M, 0.195 mol) in THF at −10 °C. The mixture was stirred at rt overnight, quenched with a solution of satd NH_4Cl to give after workup and distillation in vacuo 22.4 g (81.8%) pure **9a** of bp 100–105°C/12 Torr.

4.1.4. 5-Ethinyl-5-(tert-butyldimethylsilyloxy)-nona-1,8-diene ***9b***. To a solution of the alcohol **7a** (13.8 g, 84 mmol) and 25 mL (0.18 mol) Et_3N, in 50 mL of ice cooled THF was dropwise added 25 mL (28.78 g, 0.109 mol) TBDMS-triflate from a syringe. The mixture was stirred at rt overnight and worked up. The crude product was filtered through silica gel with hexane to give 23.0 g (98%) of pure **9b**.

4.2. Pauson–Khand-reaction with 9b

To a solution of $Co_2(CO)_8$ (33 g, 96.5 mmol) in 300 mL of THF under N_2 was added a solution of the diene/ethinyl-silyl ether **9b** (21.0 g, 75.4 mmol) in THF (100 mL). After stirring for 5 h at rt 100 g (741 mmol) 4-methylmorpholine *N*-oxide was added in small portions. The mixture was stirred at rt for 60 h, filtered through silica gel with EtOAc/hexane (1:4) to give 17.5 g of crude product. Repeated CC over silica gel with EtOAc/hexane (1:4, then 1:99 and 2:98) gave 6.9 g (29.9%) of pure *trans* product **9**, 6.0 g (26.0%) of the pure *cis*-isomer **10** and 1.1 g (4.8%) of a *cis*/*trans*-mixture of **10** and **11** isomer (total yield 60.7%).

4.2.1. cis-Isomer ***10***. R_f (ether/hexane=3:11) 0.26; IR: 2960 (vs), 2930 (vs), 2860 (s), 1703 (vs), 1635 (s), 1260 (s), 1175 (s), 1108 (s), 1062 (s), 910 (s), 835 (vs); MS: 306 (M^+, 1), 291 (2), 251 (31), 250 (31), 249 (100), 157 (35), 117 (26), 75 (74), 73 (80); ^{1}H NMR: 6.00 (d, *J*=2.2, 1H), 5.87–5.73 (m, 1H), 5.04–4.91 (m, 2H), 2.88 (m, 1H), 2.65 (dd, *J*=18.0. 6.2, 1H), 2.35–2.20 (m, 1H), 2.19–1.94 (st., 5H), 1.88–1.67 (m, 2H), 1.52–1.38 (m, 1H), 0.88 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C NMR: 210.1 (s), 194.4 (s), 138.2 (d), 124.9 (d), 114.7 (t), 80.4 (s), 43.8 (t), 42.0 (d), 41.5 (t), 40.7 (t), 28.9 (t), 28.7 (t), 25.8 (q), 18.3 (s), −2.3 (q), −2.4 (q); HR-MS: calcd For $C_{18}H_{30}O_2Si$ 306.20015, found 306.19995.

4.2.2. trans-Isomer ***11***. R_f (ether/hexane=5:14) 0.34; ^{1}H NMR: 5.93 (d, *J*=2.6, 1H), 5.89–5.73 (m, 1H), 5.07–4.91 (m, 2H), 3.27–3.16 (m, 1H), 2.67 (dd, *J*=18.0, 6.2, 1H), 2.33–1.87 (st., 7H), 1.69–1.58 (m, 1H), 1.16–1.02 (m, 1H), 0.85 (s, 9H), 0.07 (s, 3H), −0.01 (s, 3H); ^{13}C NMR: 214.4 (s), 138.1 (d), 124.0 (d), 114.6 (t), 77.6 (s), 43.9 (d), 43.0 (t), 41.4 (t), 38.9 (t), 28.5 (t), 25.6 (q), 18.1 (s), −2.8 (q), −3.0 (q).

4.2.3. rel(1R,4S,7S,10R)-7-tert-Butyldimethylsilyloxy-tetracyclo [5.4.1.0^{4,12}.0^{10,12}] dodecan-2-one (cis,cis,cis,cis-[4.5.5.5]-fenestranone) ***12***. A solution of the *cis* Pauson–Khand product **10** (3.2 g, 11 mmol) in *t*-BME (20 mL) was added to hexane (200 mL), degassed and irradiated at 254 nm with a low pressure mercury lamp for 20 h under N_2. Evaporation of the solvent and CC over silica gel with EtOAc/hexane (1:99) gave 1.4 g (44%) of the *cis*-fenestranone **12**.

R_f (hexane/EtOAc=1:1) 0.74; IR: 2950 (s), 2930 (s), 1728 (s), 834 (s); MS: 306 (M^+, 1), 250 (22), 249 (100), 157 (22), 105 (19), 75 (34); ^{1}H NMR: 2.80 (dd, *J*=10.1, 4.4, 1H), 2.51 (dd, *J*=16.5, 8.1, 1H), 2.33–2.23 (nm, 2H), 2.16–2.07 (st., 4H), 2.02–1.90 (st., 3H), 1.84 (ddd, *J*=12.5, 10.1, 5.4, 1H), 1.76–1.59 (st., 3H), 0.92 (s, 3H), 0.17 (s, 3H); ^{13}C NMR: 217.8 (s), 90.8 (s), 67.1 (s), 46.8 (t), 42.3 (d), 42.1 (d), 40.2 (d), 39.3 (t), 38.0 (t), 33.8 (t), 31.1 (t), 25.7 (q), 24.9 (t), 18.0 (s), −2.9 (q), −3.1 (q).

4.2.4. rel(1R,4R,7S,10R)-7-tert-Butyldimethylsilyloxy-tetracyclo [5.4.1.0^{4,12}.0^{10,12}]dodecan-2-one(cis,trans,cis,cis-[4.5.5.5] fenestranone) ***15***. A solution of the *trans* Pauson–Khand product **11** (3.0 g, 0.010 mol) in *t*-BME (20 mL) was added to hexane (200 mL, degassed in the ultrasound bath under Ar) and irradiated at 254 nm with a low pressure mercury lamp for 20 h under N_2. The solvent was evaporated under reduced pressure to give 3.0 g of a mixture, which was purified by CC over silica gel with 0.5% of EtOAc in hexane to give the *trans*-fenestrane **15** (1.8 g, 60%).

Mp: 58 °C; R_f (hexane/ether=3:1) 0.48; IR: 2958 (s), 1730 (vs), 1100 (s); MS: 307 (M+11, 11), 306 (25), 251 (34), 250 (44), 249 (100), 248 (49), 221 (30), 207 (37), 179 (40), 157 (78), 145 (30), 131 (53), 129 (54), 117 (37), 105 (35), 91 (35). 75 (72), 73 (56); ^{1}H NMR: 2.64 (dt, *J*=7.7, 7.6, 1H), 2.40–2.19 (st., 5H), 2.22–2.03 (m, 2H), 2.01–1.91 (st., 2H), 1.90–1.84 (m, 1H), 1.75 (ddd, *J*=12.1, 8.3, 1.8, 1H), 1.65–1.50 (m, 2H), 1.32–1.23 (m, 1H), 0.92 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR: 220.2 (s), 85.3 (s), 69.0 (s), 44.1 (t), 43.4 (d), 42.5 (d) 41.2 (t), 38.2 (t), 36.2 (d), 28.4 (t), 25.5 (t), 25.5 (q), 25.4 (t), 17.8 (s), −2.7 (q), −3.1 (q). Elemental analysis: $C_{18}H_{30}O_2Si$, calcd C 70.53, H 9.86, found C 70.56, H 9.78. For the X-ray structure of **15** see Ref. 14.

4.2.5. rel(1R,4S,7S,10R)-7-Hydroxy-tetracyclo[5.4.1.0^{4,12}.0^{10,12}] dodecan-2-one ***13***. A solution of **12** (0.58 g, 1.90 mmol) and 3 g (9.48 mmol) $(n\text{-}C_4H_9)_4N^+$ $F(\times 3H_2O)^-$ in 45 mL THF was stirred for 50 h. The organic phase, obtained after addition of H_2O and ether, was dried over $MgSO_4$ and gave after FC with hexane/EtOAc (1:1) 0.325 g (89%) **13**.

R_f (hexane/EtOAc=1:1) 0.31; IR: 3600 (w), 2940 (m), 1728 (vs), 1120 (m); MS: 193 (M^++1, 24), 192 (88), 164 (56), 163 (20), 150 (35), 149 (34), 146 (21), 138 (81), 137 (100), 135 (43), 122 (48), 109 (75), 91 (47), 79 (51); ^{1}H NMR: 2.86 (dd, J=10.2, 4.5, 1H), 2.72–2.61 (m, 1H), 2.38–1.55 (st., 14H); ^{13}C NMR: 221.7 (s), 89.2 (s), 66.2 (s), 46.4 (t), 43.0 (d), 43.0 (d), 40.6 (d), 40.1 (t), 39.5 (t), 34.0 (t), 31.8 (t), 25.6 (t); HR-MS: calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1149.

4.2.6. rel(1R,4R,7S,10R)-7-Hydroxy-tetracyclo[5.4.1.0^{4,12}.0^{10,12}] dodecan-2-one ***16***. Deprotection of **15** (0.54 g, 1.7 mmol) with 2.3 g (7.27 mmol) TBAF·3H_2O in 38 mL THF was performed as described for **12** and gave after FC (hexane/EtOAc=1:1) and crystallization in hexane 0.33 g (98%) **16** as colourless crystals.

Mp 129 °C; R_f (hexane/EtOAc=1:1) 0.30; IR: 3598 (w), 2924 (m), 1732 (vs), 1094 (m); MS: 192 (M^+, 48), 150 (41), 149 (29), 137 (44), 135 (38), 132 (100), 122 (35), 117 (45), 109 (82), 108 (42), 96 (74), 91 (58); ^{1}H NMR: 2.66–2.56 (m, 1H), 2.51 (dd, J=9.2, 0.7, 1H), 2.47–2.16 (st., 5H), 2.11–1.78 (st., 6H), 1.63–1.49 (m, 2H), 1.29–1.14 (m, 1H); ^{13}C NMR: 223.1 (s), 83.9 (s), 68.0 (s), 43.6 (t), 43.5 (d), 42.6 (d), 41.8 (t), 38.8 (t), 37.3 (d), 28.0 (t), 26.0 (t), 25.5 (t); HR-MS: calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1149.

4.2.7. rel(1R,4S,10R)-Tetracyclo[5.4.1.0^{4,12}.0^{10,12}]dodec-6-en-2-one ***20*** *and rel(1R,4S,10R)-tetracyclo[5.4.1.0^{4,12}.0^{10,12}]dodec-7-en-2-one* ***21***. Mesylchloride (0.13 g, 1.04 mmol) was added to a solution of **13** (0.1 g, 0.52 mmol), Et3N (0.263 g, 2.6 mmol) and DMAP (10 mg, 1.04 mmol) in 15 mL CH_2Cl_2 at −40 °C. After 10 min the reaction was wormed to rt and treated with 10 mg DMAP every 20 h. After 60 h the reaction mixture was poured onto ice-water and extracted with ether. The crude product was purified by CC (hexane/ether=5:1) to give 79 mg (87%) of a colourless oil, which was separated by HPLC (hexane/*t*-BME=19:1) to give pure samples the regioisomers **20** and **21**.

4.2.8. Fenestrenone ***20***. R_f (hexane/EtOAC=1:1): 0.61; HPLC: 27.5 min; IR: 2902 (m), 2888 (m), 2855 (m) 2842 (m), 1720 (vs), 1155 (m), 1110 (m);

MS: 175 (M^++1, 9) 174 (38), 119 (22), 117 (22), 105 (48), 104 (100), 103 (25), 91 (40), 78 (30), 77 (23); ^{1}H NMR: 5.27 (s, 1H), 3.02–2.89 (m, 1H), 2.85–2.72 (st., 2H), 2.63–2.34 (st., ∼6H), 2.24–2.15 (m, 1H), 2.07–1.84 (st., 3H), impurity a 1.61 (s); ^{13}C NMR: 222.63 (s), 152.15 (s), 118.15 (d), 69.86 (s), 46.97 (d), 46.46 (t), 45.59 (t), 41.37 (d), 39.00 (d), 35.04 (t), 26.34 (t), 25.02 (t); for 2D-correlations see Supplementary, Table 1; HR-MS. calcd for $C_{12}H_{14}O$ 174.1045, found 174.1020.

4.2.9. Fenestrenone ***21***. R_f (hexane/EtOAc): 0.61; HPLC: 31 min; IR 2938 (s), 2910 (m), 2895 (m), 2842 (m), 1725 (vs), 1241 (m), 1155 (m); MS: 175 (M^++1, 10), 174 (40), 119 (81), 118 (19), 117 (25), 105 (36), 104 (100), 91 (37); ^{1}H NMR: 5.41 (s, 1H), 3.09–2.98 (m, 1H), 2.86–2.79 (st., 3H), 2.69–2.60 (m, 1H), 2.46–2.36 (m, 1H), 2.36–2.20 (st. 5H), 2.10–2.00 (m, 1H), 1.72–1.61 (m, 1H), impurity at 1.60.

^{13}C NMR: 222.84 (s), 151.10 (s), 121.55 (d), 71.97 (s), 50.34 (d), 46.91 (t), 45.86 (t), 39.53 (d), 35.57 (d), 29.50 (t), 23.44 (t); for 2D-correlations see Supplementary, Table 2. HR-MS: calcd for $C_{12}H_{14}O$ 174.1045 found 174.1050.

4.2.10. rel(1R,4R,7S,10R)-7-methylsulfonato-tetracyclo-[5.4.1.0^{4,12}.0^{9,12}] dodeca-2-on ***17***. A solution of the hydroxyketone **16** (0.20 g, 1.04 mmol), triethylamine (0.54 g, 5.34 mmol) and DMAP (0.06 g, 0.5 mmol) in CH_2Cl_2 (30 mL, HPLC grade) was cooled to −40 °C and then MsCl (0.56 g, 4.48 mmol) was added dropwise during 10 min. The solution was slowly warmed to 0 °C, stirred for 3 h and allowed to reach rt overnight. The yellow solution was quenched with 100 mL of ice-water and extracted with Et_2O (80 mL). The aqueous phase was extracted with Et_2O (3×, 30 mL each) The organic phase was dried over Na_2SO_4, removed in vacuo and the brown crude product purified by flash chromatography (hexane/ether=1:2) to give **17** (70 mg, 25%) as colourless oil.

R_f: 0.46 (hexane/ether=1:2); IR: 2940 (m), 2863 (m), 1739 (vs), 1339 (vs), 1260 (m), 1173 (s), 948 (s); ^{1}H NMR: 3.54 (dd, J=8.5, 8.4, 1H), 3.28–3.17 (m, 1H), 3.08 (s, 3H), 3.09–2.99 (m, 1H), 2.45–2.35 (m, 3H), 2.33–2.23 (m, 1H), 2.25 (ddd, J=18.2, 1.9, 1.1, 1H), 2.16–1.78 (stack, 7H) 1.64–1.54 (m, 1H), 1.13–1.01 (m, 1H); ^{13}C NMR: 217.1 (s), 111.7 (s), 62.6 (s), 59.7 (q), 46.7 (d), 45.1 (d), 43.6 (t), 40.4 (d), 35.8 (t), 35.5 (t), 32.0 (t), 22.8 (t), 21.7 (t); MS 270 (M^+, 3), 242 (1), 174 (33), 146 (20), 133 (23) 132 (73), 131 (32), 117 (37), 104 (35), 97 (35), 95 (100), 91 (24); HR-MS: calcd for $C_{13}H_{16}O_4S$ 270.0921, found 270.0926.

4.2.11. 12-Trifluoromethanesulfonato-tetracyclo-[5.4.1.0^{4,12}.0^{7,10}] dodeca-2-one ***22***. A solution of the c,t,c,c-hydroxyketone **16** (0.05g, 0.26 mmol) in CH_2Cl_2 (4 mL) was treated with pyridine (0.089 g, 1.14 mmol, 4.37 mol equiv) at −2 °C. After cooling to −7 °C a solution of Tf_2O (0.117 g, 0.41 mmol, 1.59 mol equiv) was slowly added via syringe techniques, stirred for 1 h and kept overnight at −20 °C. The yellowish, neutral solution was poured onto ice-water, extracted with 10 mL of H_3PO_4 (four drops of 85% H_3PO_4 in 10 mL H_2O). The acidic solution (pH ∼3) was decanted and extracted with CH_2Cl_2 (10 mL, 2×). The organic phase was washed with H_2O (20 mL, 2×) dried over $MgSO_4$ to give after evaporation of the solvent **22** (0.075 g, 88.9%) of an almost colourless oil.

R_f 0.45 (hexane/*t*-BME=1:2), impurity at R_f 0.17. ^{1}H NMR: 3.50 (dd, J=8.1, 0.8, 1H), 3.11 (dd, J=20.2, 9.5, 1H), 2.97 (dd, J_{AB}=9.5, 1.5, 1H), 2.45–2.40 (m, 1H), 2.31–2.20 (m, 2H), 2.18–1.8 (m, 7H), 1.70–1.59 (m, 1H), 1.16–1.05 (m, 1H); ^{13}C NMR: 215.1 (s), 119.5 (s), 117 (s) (q, CF_3, J=317.2 Hz), 62.6 (s), 59.8 (d), 46.7 (d), 45.9 (d), 43.2 (t), 35.6 (t), 35 (t), 31.9 (t), 22.8 (t), 21.5 (t); for the 2D NMR data see Supplementary, Table 3. ^{19}F NMR: −75.9 (rel to CCl_3F at −78.44 ppm), (^{1}H-BB-decoupled); EI-MS: 192 ([M−CF_3SO_2]$^+$, 5), 174 (8), 132 ([CF_3SO_2]$^+$, 31), 117 (9), 109 (22), 96 (38), 95 (20), 91 (15), 83 (10), 81 (10), 79 (12), 77 (12), 69 ([CF_3]$^+$, 100), 65 (40) 64(15).

4.2.12. 12-Methoxy-tetracxyclo[5.4.1.0^{4,12}.0^{7,10}]dodecan-2-one ***23a***. A solution of the triflate **22** (0.062g, 0.19 mmol) in CH_2Cl_2 (4 mL) was treated at 0 °C with DBU (0.075 g, 0.5 mmol), Et_3N (0.064 g, 0.6 mmol) and 2 mL CH_3OH. After stirring for 105 min, the mixture was poured on ice, diluted with 10 mL CH_2Cl_2, extracted with 20 mL satd NH_4Cl (2×), washed with brine (20 mL) and dried over $MgSO_4$ to give, after evaporation of the solvent, 0.03 g (75.6%) of **23a**. A pure sample was obtained by FC (hexane/ether/CH_2Cl_2=2:1:2). R_f: 0.6 (hexane/ether/CH_2Cl_2=2:1:2); ^{1}H NMR: 3.21 (s, 3H), 2.99 (dd, J=5.8, 1.5, 1H), 2.78–2.61 (m, 2H), 2.37–2.20 (m, 3H), 2.12–1.82 (m, 6H), 1.68–1.52 (m, 2H), 1.08–0.95 (m, 1H); ^{13}C NMR: 220.2 (s), 102.8 (s), 60.2 (d), 59.5 (s), 51.9 (q) (OCH_3), 48.1 (d), 44.1 (t), 39.6 (d), 37.1 (t), 35.0 (t), 31.2 (t), 22.5 (t), 22.1 (t); for the COSY-spectrum see Supplementary Table 4. EI-MS: 207 (3.8), 206 ([M]$^+$, 28.8), 178 (16), 174 (9), 137 (14), 132 (36), 123 (39), 117 (9), 110 (100), 109 (59), 108 (16), 105 (13), 91 (23).

4.2.13. 1-^{2}H-12-methoxy-tetracxyclo[5.4.1.0^{4,12}.0^{7,10}]dodecan-2-one ***23b***. The triflate **22** (0.073 g, 0.225 mmol) was dissolved in 3 mL CH_2Cl_2 and cooled to −5°. A mixture of 0.042 g DBU (0.28 mmol) and 0.0455 g Et_3N (0.45 mmol) was added in 1 mL CH_2Cl_2, followed by 1 mL CH_3OH-d_1. After 10 min the mixture was poured onto ice/water, diluted with 10 mL CH_2Cl_2 and extracted 2× with satd NH_4Cl solution (20 mL each). The organic phase was 2× washed with H_2O, dried over $MgSO_4$ and the solvent removed in vacuo to give 0.032 g (69.5%) 23**b**. The ^{2}H NMR of the crude product revealed the exchange of the C(1)–H to ca. 81%.

CC on silica gel with hexane/*t*-BME (10:1) gave **23b**-(**C1**)-**D** as an oil, which was used for analysis. R_f=0.4 (hexane/*t*-BME=1:2); ^{1}H NMR: 3.19 (s, 3H), 3.00–2.88 (m, 0.19H), 2.75–2.59 (st., 2H),

2.35–2.20 (st., 3H), 2.10–1.75 (st., 6H), 1.68–1.52 (st., 2H), 1.06–0.94 (m, 1H), impurities at 1.25 (br), 1.20 and 0.90 (~t); ^{13}C NMR: 220.2 (s), 102.8 (s), 60.2 (d), 59.9 (s), 51.9 (q, OCH_3), 48.2 (d), 44.1 (t), 39.7 (d), 37.2 (t), 31.3 (t), 22.5 (t), 22.1 (t). The signal at 60.2 ppm is small (12.5% of the other 2d); the C(1)-D triplet is centred at 59.8 (J=20.5 Hz). ^{2}H NMR: 2.96 (s). For the data of 2D NMR see Supplementary, Table 5. MS: [$C_{13}H_{17}DO_2$ 207.137], 208 (2.5), 207 (16), 206 (2.7), 179 (12), 138 (10), 133 (28), 132 (13), 123 (35), 111 (15), 110 (100), 109 (37), 106 (11), 105 (10), 92 (16), 91 (17), 80 (13), 79 (17), 78 (13), 77 (14), 67 (11).

Simulation for $C_{13}H_{18}O_2$: 206.131=100; 207.134: 14.9%.

Details for the measurement of $C_{13}H_{17}DO_2$: 207.0964=100; 208.0993 (17.06) and 206.0897 (20.34).

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Supplementary data

The 2D NMR spectra of the compounds **20**–**22** and **23a**,**b** are compiled in the Tables 1–5. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.03.088.

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